at 20 °C with $CH_2{=}CHCO_2CH_3$ and anhydrous CsF (dried, vacuum desiccator) to effect the 1,3-dipolar cycloaddition. After 24 h, a 51% yield of cycloadduct **2** can be isolated based on starting lactam **10**. Some loss of material in the cycloaddition step is to be expected since the initially formed adduct loses a molecule of methanol under the reaction conditions. According to our previous experience, α-trimethylsilyl "onium" salts are sensitive to protiodesilylation by hydroxylic agents, and other complications involving the sensitive imidate salt **4** may also arise.

Catalytic reduction of **2** (10% Pd/C, atmospheric pressure, EtOAc) gave a single reduction product (83%), assigned stereochemistry as in **11** based on subsequent transformations. The only side product detected was the aromatized compound **12** (pyrrole hydrogens at 6.66 and 6.60 ppm), 8% after chromatography. The oily reduction product **11** spontaneously epimerized (48 h, 20 °C, neat) to a crystalline isomer **13** (mp 48–50 °C). Similar endo → exo isomerizations have been reported previously[11] among pyrrolizidine alkaloids.

Final transformations of **13** to retronecine involve a selenium-based elimination similar to that used by Robins for synthesis of supinidine.[6b] Generation of the enolate (−78 °C, LDA in THF + 5% HMPA) followed by reaction with diphenyl diselenide at −35 °C affords the selenide **14** in >95% yield. Oxidation of **14** (2 equiv of MCPBA, −78 °C, 2 h, CH_2Cl_2; add 5 equiv of Me_2S at −78 °C to destroy excess oxidant) followed by selenoxide elimination (cold selenoxide transferred dropwise into refluxing CCl_4 by cannula) gives the unsaturated ester **15** (oil, 90% from **13** after chromatography). Finally, Dibal reduction (−78 °C to room temperature; $Na_2SO_4{\cdot}10H_2O$ workup, 85%) and benzyl ether cleavage with 3 equiv of Li in liquid ammonia (5 h, −33 °C; quench with isoprene followed by solid NH_4Cl) results in crystalline *d,l*-retronecine,[12] 70% yield after sublimation.

Even though the key 1,3-dipolar cycloaddition proceeds in only 51% yield, the sequence from hydroxy lactam **8** to retronecine is quite efficient (ca. 20% overall). Related applications of nonstabilized imidate methylide cycloadditions to synthesis of five-membered nitrogen rings are being investigated.

Acknowledgment. We are grateful to Professor J. J. Tufariello (SUNY, Buffalo), Professor L. Zalkow (Georgia Institute of Technology), and Dr. A. R. Mattocks (Medical Research Council Laboratories, United Kingdom) for generously providing comparison samples or spectra of natural and synthetic retronecine. This work was supported by a grant from the National Institutes of Health (Grant CA 17918).

(11) Likhosherstov, A. M.; Kulkov, V. N.; Kochetkov, N. K. *Zh. Obshch. Khim.* **1964**, *34*, 2798.
(12) Mp 129–130 °C, twice recrystallized from acetone (lit.[3b,c] mp 130 °C).

E. Vedejs,* G. R. Martinez
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706
Received September 14, 1980

Thermal Reactions of 2,3-Diazabicyclo[2.2.0]hex-2-ene. The First Example of a Disrotatory Diazacyclobutene Ring Opening

Sir:

2,3-Diazabicyclo[2.2.0]hex-2-ene[1] (**1**) belongs to two important classes of compound, the diazabicyclo[2.2.*n*]alkenes[2,3] and the diazetines.[4-6] We report here that **1** undergoes two thermal reactions, a deazetation process which has an important bearing on the formally similar reaction of other cyclic azo compounds and a ring opening which is, to our knowledge, without precedent in diazetine chemistry.

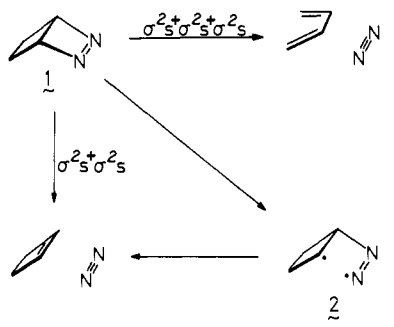

Figure 1. Possible deazetation reactions of 2,3-diazabicyclo[2.2.0]hex-2-ene.

Thermal deazetation of **1** could, in principle, give cyclobutene or butadiene as the hydrocarbon product. Unlike the deazetation of the other members of the diazabicyclo[2.2.*n*]alkene series, the concerted nitrogen extrustion from **1** is thermally forbidden[7] unless accompanied by cleavage of the C5–C6 bond (Figure 1). As always, a stepwise C-N bond cleavage could occur to afford a biradical (**2**) which would presumably lead to cyclobutene.[8]

Experimentally, pyrolysis of **1** at 90–130 °C in cyclooctane or benzene was found to give cyclobutene as the exclusive (>98%) deazetation product.[9] Some butadiene was observed at long reaction times but this could be ascribed to the known ring opening of cyclobutene.[10]

Apparently **1** eschews the ${}_\sigma2_s + {}_\sigma2_s + {}_\sigma2_s$ fragmentation, a rather suprising result when compared with pyrolysis of 3,4,5,6-tetrahydropyridazine for which the analogous three-bond cleavage comprises 46% of the reaction.[11] One might have expected that cyclobutane ring strain would have weakened the C5–C6 bond in **1** and would thereby have made the three-bond fragmentation more favorable. Possibly the higher temperature of the tetrahydropyridazine study[11] and the (presumably) positive $\Delta S^\ddagger$ for fragmentation to three components combined to make the ${}_\sigma2_s + {}_\sigma2_s + {}_\sigma2_s$ reaction more prominent in that case.

In fact deazetation was found to be only a minor reaction of **1** (~10%) in the temperature range of our investigation (90–130 °C). The main reaction was a ring opening leading, we believe, to 4,5-dihydropyridazine (**3**) as the primary product. Under the reaction conditions **3** apparently dimerized and, eventually, trimerized[12] (Figure 2) as it has been shown to do in an earlier investigation.[13]

The ^1H NMR spectrum of the reaction mixture during pyrolysis

(1) Wildi, E. A.; Carpenter, B. K. *Tetrahedron Lett.* **1978**, 2469.
(2) Boyd, R. J.; Bunzli, J. C.; Synder, J. P.; Heyman, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6478.
(3) Heyman, M. L.; Bandurco, V. T.; Synder, J. P. *Chem. Commun.* **1971**, 297.
(4) Rieber, N.; Alberts, J.; Lipsky, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 5668.
(5) Engel, P. S.; Hayes, R. A.; Keifer, L.; Szilagyi, S.; Timberlake, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 1876.
(6) White, D. K.; Greene, F. D. *J. Am. Chem. Soc.* **1978**, *100*, 6760.
(7) White and Greene[6] have raised the possibility of a fragmentation which is antarafacial on nitrogen. We do not believe that **1** would be able to undergo such a reaction because of its rigidity.
(8) Formation of butadiene from **2** would require the intermediacy of a second biradical whereas formation of cyclobutene simply involves C–N bond cleavage.
(9) Cyclobutene was identified by comparison of its ^1H NMR spectrum and GC retention time with those of an authentic sample and by its quantitative conversion to butadiene on extended pyrolysis.
(10) Cooper, W.; Walters, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 4220.
(11) Dervan, P. B.; Santilli, D. S. *J. Am. Chem. Soc.* **1980**, *102*, 3863.
(12) The trimer was identified by X-ray crystallographic analysis.[13] The dimer was unstable and could not be fully characterized but it did have a chemical ionization mass spectrum with the correct molecular ion.
(13) Bandlish, B. K.; Brown, J. N.; Timberlake, J. W.; Trefonas, L. M. *J. Org. Chem.* **1973**, *38*, 1102. We are grateful to a referee for bringing this obviously important reference to our attention.

0002-7863/80/1502-7994$01.00/0

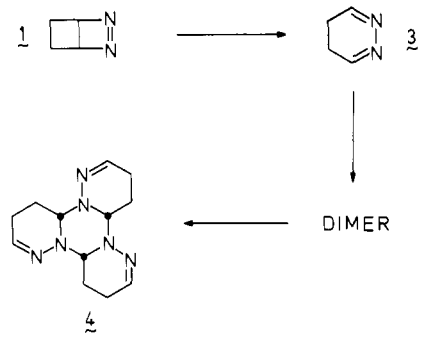

Figure 2. Observed ring-opening reaction of 2,3-diazabicyclo[2.2.0]-hex-2-ene.

of **1** was quite complex at short reaction times and did not allow unambiguous identification of **3**. Attempts to trap **3** in a Diels–Alder reaction with *N*-phenylmaleimide, *N*-phenyltriazolinedione, or dimethyl acetylenedicarboxylate all led to inconclusive results. In particular no 1:1 adducts of **3** and the dienophile could be isolated. However, two experimental observations provided, we believe, significant support for the intermediacy of **3**. First, the conversion of **1** to dimer + trimer showed clean first-order kinetics (vide infra) from $t = 0$ to $>12t_{1/2}$. Second, pyridazine could be detected[14] after **1** had been pyrolyzed to about 50% conversion, cooled to room temperature, and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). DDQ does not produce pyridazine from **1** at room temperature.

A kinetic analysis of both the deazetation and ring-opening reactions was undertaken. Product compositions were determined at temperatures between 90 and 130 °C while rate constants were evaluated between 90.5 and 120.3 °C in C_6D_6 and between 93.1 and 123.0 °C in cyclooctane. Analyses were carried out by ^1H NMR spectroscopy, using multiple integrations on sealed, degassed samples. Integration against an internal standard (*p*-dichlorobenzene) was used for calculation of the rate constants and also served to confirm that butadiene (from ring opening of the cyclobutene) and the trimer (**4**), the only detectable final products, conformed to the expected mass balance. The ratio of butadiene to **4** varied from 7:93 at 90 °C to 13:87 at 130 °C. The reactions run in C_6D_6 allowed direct measurement of the rate constants for disappearance of **1** and for formation of cyclobutene (+ butadiene). Subtraction of these numbers gave the rate constant for conversion of **1** to **4** (+ the dimer). These rate constants are reported in Table I. The activation parameters calculated from these data are $\Delta H^{\ddagger} = 32.9 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = 4.1 \pm 1.4$ cal/(mol K) for deazetation of **1** to cyclobutene and $\Delta H^{\ddagger} = 29.2 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = -2.4 \pm 1.0$ cal/(mol K) for the conversion of **1** to the trimer **4**.

The pyrolysis in cyclooctane allowed measurement of the rate constant for cyclobutene formation but did not permit an accurate determination of the ring-opening rate constant because of overlapping resonances between **1** and the dimer. The rate constants for cyclobutene formation were $(9.67 \pm 0.68) \times 10^{-7}$ s^{-1} at 93.13 °C, $(1.33 \pm 0.13) \times 10^{-5}$ s^{-1} at 115.31 °C, and $(3.27 \pm 0.29) \times 10^{-5}$ s^{-1} at 123.03 °C. These results correspond to the activation parameters $\Delta H^{\ddagger} = 33.0 \pm 0.6$ kcal/mol, $\Delta S^{\ddagger} = 3.5 \pm 1.1$ cal/(mol K).

In order to determine how the activation parameters for ring opening of **1** to 4,5-dihydropyridazine (**3**) are related to those for the overall conversion **1** → **4** it is necessary to know the mechanism of trimer formation. We feel that the two most plausible mechanisms are those summarized in A and B below:

$$\mathbf{1} \xrightarrow{k_1} \mathbf{3}; \quad \mathbf{3} + \mathbf{3} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{dimer}; \quad \text{dimer} + \mathbf{3} \xrightarrow{k_3} \mathbf{4} \qquad \text{(A)}$$

$$\mathbf{1} \xrightarrow{k_1} \mathbf{3}; \quad \mathbf{1} + \mathbf{3} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{dimer}; \quad \text{dimer} + \mathbf{1} \xrightarrow{k_3} \mathbf{4} \qquad \text{(B)}$$

(14) Pyridazine was identified by comparison of its characteristic ^1H NMR spectrum with that of an authentic sample.

Table I. Kinetic Data for Pyrolysis of 1 in C_6D_6

temp, °C	rate constant for 1 → cyclobutene, s^{-1}	rate constant for 1 → 4, s^{-1}
90.51 ± 0.01	$(5.44 \pm 0.11) \times 10^{-7}$	$(7.25 \pm 0.07) \times 10^{-6}$
101.35 ± 0.03	$(2.06 \pm 0.12) \times 10^{-6}$	$(2.43 \pm 0.07) \times 10^{-5}$
110.25 ± 0.02	$(5.60 \pm 0.34) \times 10^{-6}$	$(6.35 \pm 0.18) \times 10^{-5}$
120.25 ± 0.03	$(1.82 \pm 0.13) \times 10^{-5}$	$(1.59 \pm 0.05) \times 10^{-4}$

The ring-opening reaction (**1** → **3**) is shown as irreversible on the basis of an experimental observation: pyrolysis of 2,3-diazabicyclo[2.2.0]hex-2-ene-5,6-*exo*,*exo*-d_2[15] (**1**-d_2) to partial completion. No evidence for exo–endo isomerism of this cis-deuterium pair could be found. Irreversibility of the trimer formation was demonstrated by pyrolyzing a mixture of d_0 and d_6 trimers under the reaction conditions (in benzene). Mass spectrometry gave no evidence for the formation of d_2 or d_4 trimers.

Mechanism A relates the experimental rate constant for conversion of **1** → **4** (k_{obsd}) to the mechanistic rate constant for ring opening (k_1) by the simple equality $k_1 = k_{obsd}$. For mechanism B the relationship is $k_1 = 0.5k_{obsd}$, provided that $d[\mathbf{3}]/dt \simeq 0$ and $2k_1 \gg k_3[\text{dimer}]$ (both conditions being necessary for mechanism B to fit the observed first-order kinetics, since the dimer is clearly not a steady-state intermediate).

Experimentally, the ^1H NMR spectrum of the d_6 trimer (prepared from **1**-d_2) could best be explained by a completely random exo/endo distribution of the cis-deuterium pairs.[16] This is the expected result for mechanism A but not for mechanism B (or any other mechanism that incorporates **1** without prior ring opening to **3**). Secondary stereochemical isomerism of the trimer would require complete dissociation of a dihydropyridazine unit and is therefore ruled out by the failure to detect crossover products from $d_0 + d_6$ trimers. An acid-catalyzed mechanism seems unlikely since the reaction was unaffected by the addition of diisopropylamine (0.2 equiv). The data appear most consistent with mechanism A. This mechanism is further supported by the observation[13] that preparation of 4,5-dihydropyridazine by an independent route, not involving **1**, also resulted in trimer formation.

We assume, therefore, that the activation parameters for the conversion of **1** → **4** are, in fact, those for the ring-opening step (**1** → **3**). It is of interest to compare these data with the activation parameters for the (presumably) analogous ring opening of bicyclo[2.2.0]hex-2-ene ($\Delta H^{\ddagger} = 32.15 \pm 0.09$ kcal/mol, $\Delta S^{\ddagger} = 2.4 \pm 0.2$ cal/(mol K)).[17] One must be somewhat cautious about the comparison since the hydrocarbon data were obtained in the gas phase, but it does appear that replacement of the CH groups of the cyclobutene ring by N has a relatively small effect ($\Delta\Delta H^{\ddagger} = -3.0 \pm 0.5$ kcal/mol, $\Delta\Delta G^{\ddagger}(110\ °C) = -1.1 \pm 0.6$ kcal/mol) on the activation barrier to disrotatory ring opening. This result stands in apparent contrast to the disrotatory ring closure of 2,3-naphthoquinodimethanes where 1,4-aza substitution reduces the activation energy by 12 ± 6 kcal/mol.[18] It appears that further experimental and theoretical studies will be necessary in order to fully understand the effects of skeletal atom substitution on the rates of thermal pericyclic reactions.[19,20]

(15) **1**-d_2 was prepared in the manner previously described for **1**[1] except that D_2 was used in place of H_2.

(16) The doublet of doublets at δ 3.65 (C_6D_6) in the ^1H NMR spectrum of the d_0 trimer[13] is ascribed to the three equivalent methine hydrogens on the hexahydrotriazine ring. In the d_6 trimer there should be two separate doublet resonances with $J = 3.0$ Hz and $J = 7.5$ Hz at this position. The area ratio of these two doublets should give the ratio of endo to exo deuterium at the adjacent carbon. In reality the two doublets occur at slightly different chemical shifts ($\Delta\delta = 0.004$) apparently because of differential β-isotope effects. As a result the ^2H ^1H NMR spectrum more resembles a triplet than a pair of doublets. Nevertheless integration of the components of the multiplet is still consistent only with equal amounts of exo and endo deuterium.

(17) Goldstein, M. J.; Leight, R. S.; Lipton, M. S. *J. Am. Chem. Soc.* **1976**, *98*, 5717.

(18) Steiner, R. P.; Miller, R. D.; Dewey, H. J.; Michl, J. *J. Am. Chem. Soc.* **1979**, *101*, 1820.

(19) For another recent report of a heterocyclobutene ring opening see: Martino, P. C.; Shevlin, P. B. *J. Am. Chem. Soc.* **1980**, *102*, 5429.

(20) For an important theoretical contribution that has been made already see: Synder, J. P. *J. Org. Chem.* **1980**, *45*, 1341 and references therein.

Acknowledgment. We thank the National Science Foundation (Grants CHE-7725757 and CHE-8007986) for support of this work. We also gratefully acknowledge the cooperation of Professor Jon Clardy in allowing one of us (D.V.E.) time to work on this problem. D.V.E. thanks the National Institute of Health for Support.

Eva A. Wildi, Donna Van Engen, Barry K. Carpenter*

Department of Chemistry, Baker Laboratory Cornell University, Ithaca, New York 14853

Received August 11, 1980

Book Reviews

Semisynthetic Proteins. By R. E. Offord (Oxford University). John Wiley and Sons, Inc., New York. 1980. xi + 235 pp. $46.75.

The purposes of this book are to consolidate technical advances in the young field of protein semisynthesis and to encourage further development. The book is intended to serve both those now working in the field and those who might come to it with special skills in classical peptide chemistry or pharmacology, synthetic organic chemistry, or protein chemistry. The objective of the technique is to employ natural proteins as much as possible as the starting materials for obtaining proteins of sequences that are not found in nature. The new products, combining natural sequence segments with artificially inserted amino acid residues, provide unique opportunities for studies of protein structure and function or for labeling molecules for metabolic studies. Two or more cleaved fragments of a protein may associate noncovalently to form a functional complex, making possible noncovalent semisynthesis involving substitutions in relatively simple segments of the complete molecule, or facilitating the apposition of residues to be recoupled in the covalent semisynthesis. The field presents special problems of solubility, and irreversible aggregation pervading all stages of group protection, cleavage, activation, coupling, deprotection, and purification.

The book is organized to deal clearly with overall strategy while concentrating on technical problems. The reader is carried through all the procedural steps that are normally required, from the formal reactions to specific detailed examples of their application complete with notes dealing with alternatives, warnings, and so on. The skillful organization of disparate material from different laboratories is impressive. Particularly valuable are the illustrations of the use of enzymes in activation and coupling as well as in cleavage stages. Two appendixes deal with characterization of products and intermediates and some common technical problems. The final chapter of the text reviews briefly the findings and implications of published work on semisynthesis. Many of the most encouraging and significant results in the field have appeared since this book was completed. We may look forward to the solution of important biological questions in which the impetus of Offord's book will play no small part.

Frank R. N. Gurd, *Indiana University*

Dynamic Heterogeneous Catalysis. By K. Tamaru (University of Tokyo). Academic Press, London. 1978. xiii + 140 pp.

Many of the techniques that have been developed to study solid catalysts must be applied under conditions far removed from those actually used in catalytic reactions. Frequently they require static experimental systems. In most cases these constraints severely limit their utility in catalysis, since catalytic reactions are obviously dynamic in nature. As the author correctly asserts, "Dynamic behavior should be studied in a dynamic manner."

For over a quarter of a century Professor Tamaru has been in the process of developing techniques that can be applied in a dynamic way by perturbing systems under reaction conditions and observing their decay back to steady state. He has treated catalytic reactions as chain reactions with the catalyst being the chain carrier. This short book gives an excellent overview of the spectroscopic approach he has taken in applying this philosophy productively in his research. As a result of his and similar studies, it is now possible to understand the detailed mechanisms of several classical catalytic reactions. These are presented in such a lucid way as to make this book useful reading for both beginners and long-time practitioners of catalytic science.

The general rules that govern catalytic reactions are clearly outlined in Chapter 1. Of primary importance is the interaction between thermodynamic and kinetic parameters. Series/parallel reaction networks are illustrated by the equilibration of water in standpipes connected by different sized tubes. His treatment of the stoichiometric number concept for determining the rate-limiting step in catalytic reactions follows this analogy and is quite easily understood. A discussion of the kinetics of chain reactions and the importance of chemical intermediates conclude the chapter.

At least one component in a chemical system reacting over a solid catalyst must be adsorbed. Chapter 2 discusses a variety of techniques that are used to study directly the chemical nature of adsorbed species as well as the mathematical equations that describe the amounts of material adsorbed at equilibrium. Schematic diagrams of equipment and sample spectra make it easy to understand the application of field emission microscopy, LEED, ELS, Auger, XPS, spectrophotometry, NMR, and ESR to investigate the nature of adsorbent–adsorbate chemical bonds.

Heterogeneous kinetics and its use to help elucidate the mechanisms of catalytic reactions are covered in Chapter 3. Langmuir–Hinshelwood equations are derived, and the Temkin–Pyzhev equation for ammonia synthesis over a doubly promoted iron catalyst is cited as a classic example of dynamic behavior during catalytic reactions. The decomposition of germanium hydride and of ammonia (over a tungsten catalyst) illustrate the kinetic equations.

The real meat of the book lies in Chapter 4 where Tamaru discusses application of spectroscopic techniques to the dynamic treatment of adsorbed species under reaction conditions. Several reactions (H_2–D_2 exchange, olefin isomerization, formic acid decomposition, water–gas shift, and methanol decomposition) over zinc oxide and magnesium oxide serve to illustrate how IR and microwave spectroscopy are successfully utilized under dynamic conditions. A heavy emphasis is placed on the use of isotopic tracers to establish how atoms in adsorbed species are replaced with atoms from the gas phase. These results give an insight into the intricate details of processes that occur on the surface during catalytic reactions.

This book is quite well written. Considering its brevity, the book does an incredible job of meshing time-tested fundamental principles with the latest in current understanding of heterogeneous catalysis. It will serve as stimulating and useful reading for both catalytic neophytes and pros alike.

Joe W. Hightower, *Rice University*

Analytical Atomic Absorption Spectroscopy. By John C. VanLoon (University of Toronto). Academic Press, New York. 1980. 337 pp. $35.00

The author states in his preface that this book is designed with the practicing analyst in mind and that theory has been presented in a fairly descriptive, nonrigorous way. In our opinions, the author has succeeded admirably in meeting these goals and has produced a reference text which should prove useful to most individuals using atomic absorption as a routine method of analysis.

Although the book is written principally for workers already familiar with atomic absorption, an introductory chapter (76 pages) describes the fundamental principals of the technique and offers useful suggestions on its practical application. The instrumental components of an atomic absorption spectrophotometer are described in detail and alternative choices for each component (i.e., flames versus electrothermal atomizers) critically appraised. An interesting section is included which establishes guidelines for selecting a commercial atomic absorption spectrometer and helpful hints are included on how solutions can best be prepared and stored for use in routine analyses.

Later chapters deal with the analysis of various samples by kind. For example, Chapter Two deals with the analysis of waters, whereas later chapters cover geological materials, organic samples, metals and alloys, air samples, petroleum and petroleum products, and metal compounds. In each chapter, a number of methods are included for specific samples of that kind and procedures for commonly determined elements are detailed. Each of the particular methods is presented in the following basic format:

Comment on the method—In this section the inadequacies of the